FIG. 1

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FIG. 2

RECEIVE ROUTINE

START

PROMPT USER FOR LOCATION OF DATA VALUES TO BE RECEIVED
100

RECEIVE AND STORE KINASE DATA IN INPUT DATA STORE
108

PROMPT USER FOR SELECTION OF DESIRED ANALYSIS
129

COEXPRESSION SELECTED?
131

— Y →

GO TO COEXPRESSION ROUTINE
133

N

COREGULATION SELECTED?
135

— Y →

GO TO COREGULATION ROUTINE
137

N

LINKAGE SELECTED?
139

— Y →

GO TO LINKAGE ROUTINE
141

N

TIMEOUT?
143

N

36

FIG. 3

| KINASE | PHOS. STATE | PHYSICAL PROPERTY VALUES IN EACH MODEL SYSTEM | | | | | | | | | |
		1	2	3	4	5	6	7	8	9	10
A	P	85	0	0	0	0	0	360	255	0	0
	D	0	180	142.5	160	100	95	0	0	200	90
B	P	22.5	0	0	0	0	0	85	75	0	0
	D	0	42.5	37.5	50	25	25	0	0	47.5	25
C	P	50	95	0	0	0	0	200	127.5	100	42.5
	D	0	0	63.75	100	47.5	50	0	0	0	0
D	P	190	400	0	0	0	0	800	600	300	200
	D	0	0	300	400	200	200	0	0	0	0
E	P	0	127.5	0	142.5	0	0	0	6.2	0	3.75
	D	67.5	0	112.5	0	75	75	225	6.25	0	3.75
F	P	0	50	0	50	0	0	0	0	1.3	0
	D	25	0	37.5	0	25	25	100	0	1.2	0
G	P	0	212.5	0	6.3	0	0	12.5	0	0	0
	D	112.5	0	187.5	250	6.2	0	12.5	0	0	0
H	P	0	100	0	0	0	0	14.5	0	2.5	1.2
	D	50	0	67.5	90	0	0	15.5	0	2.5	1.3
I	P	0	0	225	255	150	0	0	450	0	7.5
	D	0	0	0	0	0	150	540	0	0	7.5
J	P	0	18.75	159.4	250	125	0	0	318.8	0	0
	D	0	18.75	0	0	0	125	475	0	0	0
K	P	1.9	0	112.5	142.5	63.8	75	270	225	0	0
	D	1.85	0	0	0	0	0	0	0	0	0
L	P	0	0	75	100	45	50	200	142.5	2.6	2.4
	D	0	0	0	0	0	0	0	0	2.4	2.6
M	P	0	0	0	0	100	85	400	0	10	0
	D	0	0	0	0	0	0	0	300	10	0
N	P	2.5	2.5	0	0	25	25	100	0	0	0
	D	2.5	2.5	0	0	0	0	0	75	0	0
O	P	0	0	4.7	6.25	106.3	125	475	0	19	6.4
	D	0	0	4.7	6.25	0	0	0	318.75	18.5	6.1
P	P	0	0	0	0	150	142.5	600	0	0	0
	D	0	0	0	0	0	0	0	450	0	0
Q	P	0	0	5.625	0	0	0	0	8	100	42.5
	D	50	85	5.6	0	0	0	0	7	0	0
R	P	0	0	0	5	0	5	15	0	190	100
	D	100	200	0	5	0	5	15	0	0	0
S	P	0	0	0.95	0	1.2	0	0	0	42.5	22.5
	D	21.25	50	0.95	0	1.3	0	0	0	0	0
T	P	0	0	0	0	0	0	15	0	250	118.75
	D	125	225	0	0	0	0	15	0	0	0
Erk1	P	0	0	0	0	0	0	0	0	0	0
	D	50	100	75	100	50	50	200	150	100	50

Reference labels: 112, 114, 120, 122, 126, 124, 202, 54, 116, 118

FIG. 4

COEXPRESSION ROUTINE

START

PRODUCE TOTAL AMOUNT PER KINASE VALUES, STORE IN TPK DATA STORE 56
130

FOR EACH DATA SET, NORMALIZE ALL TOTAL AMOUNTS RELATIVE TO REFERENCE KINASE, STORE NORMALIZED VALUES IN 1ST NORMALIZED DATA STORE
138

FOR EACH KINASE, NORMALIZE ALL NORMALIZED TOTAL AMOUNTS RELATIVE TO MAXIMUM TOTAL FOR THAT KINASE, STORE IN 2ND NORMALIZED DATA STORE
150

FOR EACH PAIR OF KINASES (K1, K2), PRODUCE COEXPRESSION COEFFICIENT

$$CEC(K1,K2) = \frac{\sum_{i=1}^{N} (Q_{iK1} - Q_{iK2})}{N}$$,STORE

156

PRODUCE LIST OF COEXPRESSED KINASE PAIRS (K1,K2) FOR WHICH CEC(K1,K2) $\leq$ THRESHOLD
168

CALL CLUSTERING SUBROUTINE
174

OUTPUT COEXPRESSED PAIRS, CLUSTERS
176

END

40

FIG. 5

TOTAL PER PROTEIN (TPP) DATA STORE

SYSTEM KINASE	1	2	3	4	5	6	7	8	9	10
A	85	180	142.5	160	100	95	360	255	200	90
B	22.5	42.5	37.5	50	25	25	85	75	47.5	25
C	50	95	63.75	100	47.5	50	200	127.5	100	42.5
D	190	400	300	400	200	200	800	600	300	200
E	67.5	127.5	112.5	142.5	75	75	255	11.25	0	7.5
F	25	50	37.5	50	25	25	100	0	2.5	0
G	112.5	212.5	187.5	250	12.5	0	25	0	0	0
H	50	100	67.5	90	0	0	30	0	5	2.5
I	0	0	225	255	150	150	540	450	0	15
J	0	37.5	159.4	250	125	125	475	318.8	0	0
K	3.75	0	112.5	142.5	63.8	75	270	225	0	0
L	0	0	75	100	45	50	200	142.5	5	5
M	0	0	0	0	100	85	400	300	20	0
N	5	5	0	0	25	25	100	75	0	0
O	0	0	9.4	12.5	106.3	125	475	318.75	37.5	12.5
P	0	0	0	0	150	142.5	600	450	0	0
Q	50	85	11.25	0	0	0	0	15	100	42.5
R	100	200	0	10	0	10	30	0	190	100
S	21.25	50	1.9	0	2.5	0	0	0	42.5	22.5
T	125	225	0	0	0	0	30	0	250	118.75

| Erk 1 | 50 | 100 | 75 | 100 | 50 | 50 | 200 | 150 | 100 | 50 |

132   134   136   140   142   144   56

FIG. 6

FIRST NORMALIZED DATA STORE

151

146

SYSTEM KINASE	1	2	3	4	5	6	7	8	9	10	MAX VALUE
A	170	180	190	160	200	190	180	170	200	180	200
B	45	42.5	50	50	50	50	42.5	50	47.5	50	50
C	100	95	85	100	95	100	100	85	100	85	100
D	380	400	400	400	400	400	400	400	300	400	400
E	135	127.5	150	142.5	150	150	127.5	7.5	0	15	150
F	50	50	50	50	50	50	50	0	2.5	0	50
G	225	212.5	250	250	25	0	12.5	0	0	0	250
H	100	100	90	90	0	0	15	0	5	5	100
I	0	0	300	255	300	300	270	300	0	30	300
J	0	37.5	212.5	250	250	250	237.5	212.5	0	0	250
K	7.5	0	150	142.5	127.5	150	135	150	0	0	150
L	0	0	100	100	90	100	100	95	5	0	100
M	0	5	0	0	200	170	200	200	20	10	200
N	10	0	0	0	50	50	50	50	0	0	50
O	0	0	12.5	12.5	212.5	250	237.5	212.5	37.5	25	250
P	0	0	0	0	300	285	300	300	0	0	300
Q	100	85	15	0	0	0	0	10	100	85	100
R	200	200	0	10	0	20	15	0	190	200	200
S	42.5	50	2.5	0	5	0	0	0	42.5	45	50
T	250	225	0	0	0	0	15	0	250	237.5	250

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FIG. 7

SECOND NORMALIZED DATA STORE

SYSTEM KINASE	1	2	3	4	5	6	7	8	9	10
A	85	90	95	80	100	95	90	85	100	90
B	90	85	100	100	100	100	85	100	95	100
C	100	95	85	100	95	100	100	85	100	85
D	95	100	100	100	100	100	100	100	75	100
E	90	85	100	95	100	100	85	5	0	10
F	100	100	100	100	100	100	100	0	5	0
G	90	85	100	100	10	0	5	0	0	0
H	100	100	90	90	0	0	15	0	5	5
I	0	0	100	85	100	100	90	100	0	0
J	0	15	85	100	100	100	95	85	5	10
K	5	0	100	95	85	100	90	100	0	0
L	0	0	100	100	90	85	100	95	5	10
M	0	0	0	0	100	100	100	100	10	0
N	10	5	0	0	100	100	100	100	0	0
O	0	0	5	5	85	100	95	85	15	10
P	0	0	0	0	100	95	100	100	0	0
Q	100	85	15	0	0	0	0	10	100	85
R	100	100	0	0	0	10	7.5	0	95	100
S	85	100	5	5	10	0	0	0	85	90
T	100	90	0	0	0	0	6	0	100	95

152   154   158   160   60

FIG. 8

COEXPRESSION COEFFICENTS STORE

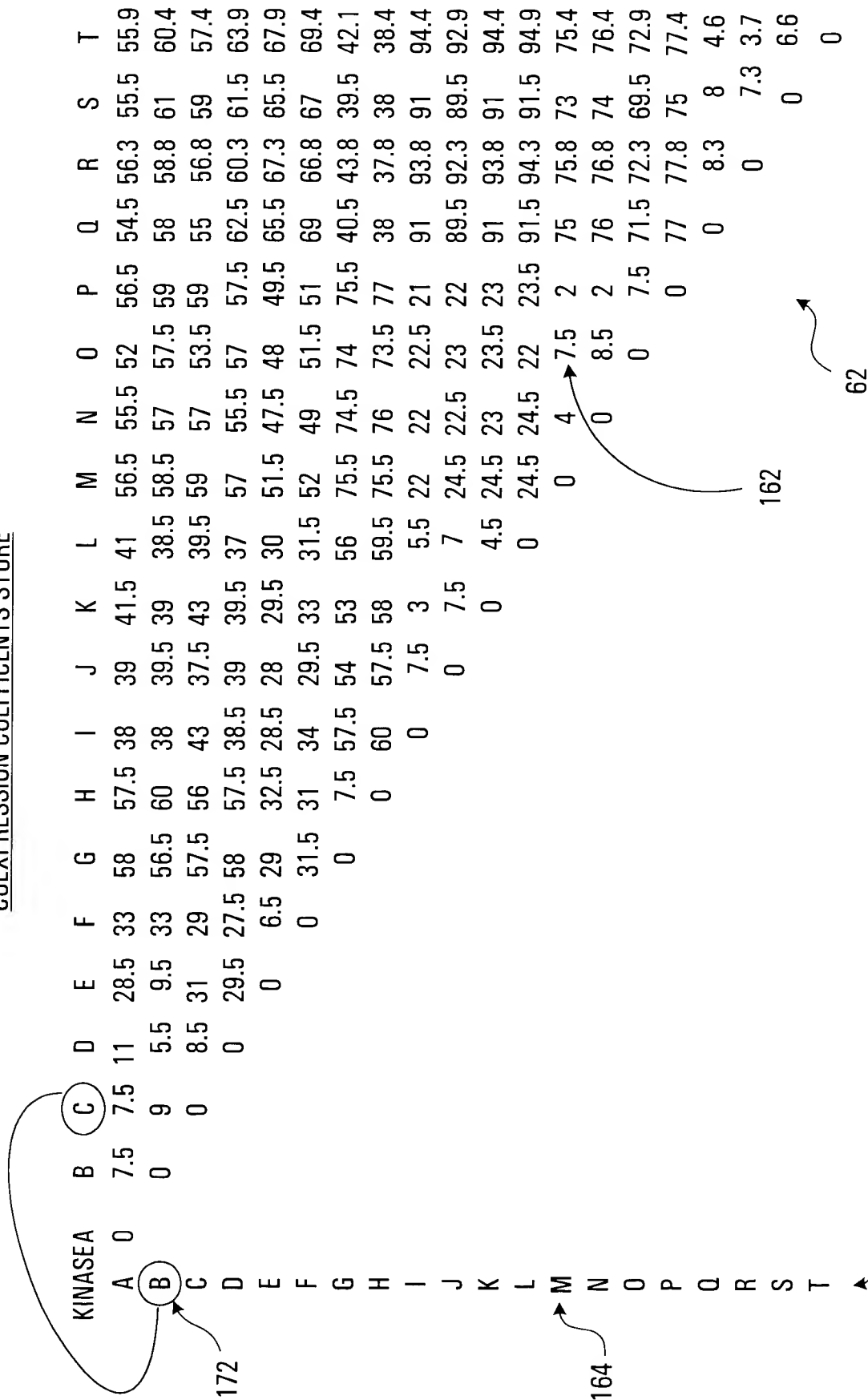| KINASE	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
A	0	7.5	7.5	11	28.5	33	58	57.5	38	39	41.5	41	56.5	55.5	52	56.5	54.5	56.3	55.5	55.9
B		0	9	5.5	9.5	33	56.5	60	38	39.5	39	38.5	58.5	57	57.5	59	58	58.8	61	60.4
C			0	8.5	31	29	57.5	56	43	37.5	43	39.5	59	57	53.5	59	55	56.8	59	57.4
D				0	29.5	27.5	58	57.5	38.5	39	39.5	37	57	55.5	57	57.5	62.5	60.3	61.5	63.9
E					0	6.5	29	32.5	28.5	28	29.5	30	51.5	47.5	48	49.5	65.5	67.3	65.5	67.9
F						0	31.5	31	34	29.5	33	31.5	52	49	51.5	51	69	66.8	67	69.4
G							0	7.5	57.5	54	53	56	75.5	74.5	74	75.5	40.5	43.8	39.5	42.1
H								0	60	57.5	58	59.5	75.5	76	73.5	77	38	37.8	38	38.4
I									0	7.5	3	5.5	22	22	22.5	21	91	93.8	91	94.4
J										0	7.5	7	24.5	22.5	23	22	89.5	92.3	89.5	92.9
K											0	4.5	24.5	23	23.5	23	91	93.8	91	94.4
L												0	24.5	24.5	22	23.5	91.5	94.3	91.5	94.9
M													0	4	7.5	2	75	75.8	73	75.4
N														0	8.5	2	76	76.8	74	76.4
O															0	7.5	71.5	72.3	69.5	72.9
P																0	77	77.8	75	77.4
Q																	0	8.3	8	4.6
R																		0	7.3	3.7
S																			0	6.6
T																				0

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162

172

164

166

FIG. 9

COEXPRESSED PAIRS STORE

170

A+B, A+C, A+D
B+C, B+D, B+E
C+D
E+F
G+H
I+K, I+L, I+J
J+K, J+L
K+L
M+N, M+O, M+P
N+O, N+P
O+P
Q+R, Q+S, Q+T
R+S, R+T
S+T

64

FIG. 10

COEXPRESSED CLUSTERS STORE

188

1. A+B, A+C, A+D, B+C, B+D, C+D
2. J+K, J+L, K+L, I+J, I+K, I+L
3. M+N, M+O, M+P, N+O, N+P, O+P
4. Q+R, Q+S, Q+T, R+S, R+T, S+T

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FIG. 11

CLUSTERING SUBROUTINE

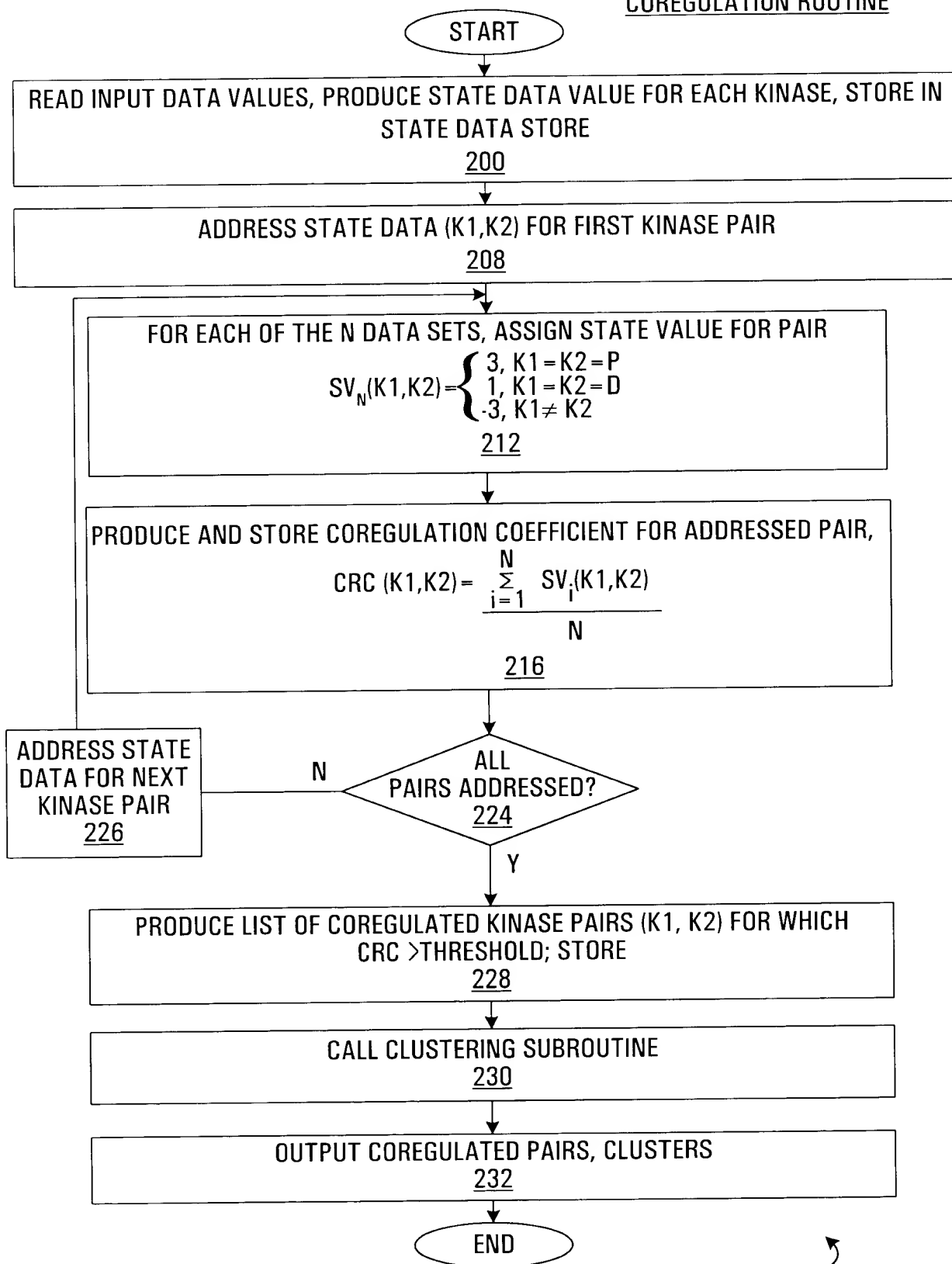(START)

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ADDRESS 1ST KINASE PAIR IN PAIRS STORE IDENTIFIED BY CALLING ROUTINE (COEXPRESSION OR COREGULATION)
180

PRODUCE NEW CLUSTER LIST, ADD ADDRESSED PAIR TO LIST
182

OTHER PAIRS IN PAIRS STORE INCLUDE AT LEAST ONE KINASE IN LIST?
184

Y → ADD SUCH PAIRS TO LIST 186

N

ANY PAIR IN LIST HAS AT LEAST ONE KINASE NOT IN ANY OTHER PAIR IN LIST?
190

Y → DELETE SUCH PAIR FROM LIST 192

N

FIG. 12

CLUSTER LIST PRODUCED FOR EACH PAIR IN PAIRS STORE?
194

Y → DELETE REDUNDANT CLUSTER LISTS FROM CLUSTER STORE 196

COPY CLUSTER STORE TO DATA STORAGE 198

N

ADDRESS NEXT PAIR IN PAIRS STORE
195

(RETURN)

COREGULATION ROUTINE

START

READ INPUT DATA VALUES, PRODUCE STATE DATA VALUE FOR EACH KINASE, STORE IN STATE DATA STORE
200

ADDRESS STATE DATA (K1,K2) FOR FIRST KINASE PAIR
208

FOR EACH OF THE N DATA SETS, ASSIGN STATE VALUE FOR PAIR

$$SV_N(K1,K2) = \begin{cases} 3, & K1=K2=P \\ 1, & K1=K2=D \\ -3, & K1 \neq K2 \end{cases}$$

212

PRODUCE AND STORE COREGULATION COEFFICIENT FOR ADDRESSED PAIR,

$$CRC(K1,K2) = \frac{\sum_{i=1}^{N} SV_i(K1,K2)}{N}$$

216

ALL PAIRS ADDRESSED?
224

ADDRESS STATE DATA FOR NEXT KINASE PAIR
226

N

Y

PRODUCE LIST OF COREGULATED KINASE PAIRS (K1, K2) FOR WHICH CRC >THRESHOLD; STORE
228

CALL CLUSTERING SUBROUTINE
230

OUTPUT COREGULATED PAIRS, CLUSTERS
232

END

FIG. 13

42

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STATE DATA STORE

SYSTEM KINASE	1	2	3	4	5	6	7	8	9	10
A	P	D	D	D	D	D	P	P	D	D
B	P	D	D	D	D	D	P	P	D	D
C	P	P	D	D	D	D	P	P	P	P
D	P	P	D	P	D	D	P	P	P	P
E	D	P	D	P	D	D	D	N.S.	N.S.	N.S.
F	D	P	D	D	D	D	D	N.S.	N.S.	N.S.
G	D	P	D	P	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
H	D	P	P	P	P	D	D	P	N.S.	N.S.
I	N.S.	N.S.	P	P	P	D	D	P	N.S.	N.S.
J	N.S.	N.S.	P	P	P	P	D	P	N.S.	N.S.
K	N.S.	N.S.	P	P	P	P	P	P	N.S.	N.S.
L	N.S.	N.S.	P	P	P	P	P	D	N.S.	N.S.
M	N.S.	N.S.	N.S.	N.S.	P	P	P	D	N.S.	N.S.
N	N.S.	N.S.	N.S.	N.S.	P	P	P	D	N.S.	N.S.
O	D	D	N.S.	N.S.	P	P	P	D	P	P
P	D	D	N.S.	N.S.	P	P	P	D	P	P
Q	D	D	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	P	P
R	D	D	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	P	P
S	D	D	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	P	P
T	D	D	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	P	P

204   206   214   210

FIG. 14

COREGULATION COEFFICIENTS STORE

KINASE	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
A	0	1.6	0.4	0.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B		0	0.4	0.4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C			0	2.2	0	0	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0
D				0	0	0	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0
E					0	1.57	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0
F						0	0.5	0.5	0	0	0	0	0	0	0	0	0	0	0	0
G							0	1.5	0	0	0	0	0	0	0	0	0	0	0	0
H								0	0	0	0	0	0	0	0	0	0	0	0	0
I									0	2.33	1.0	1.0	0	0	0	0	0	0	0	0
J										0	1.0	1.0	0	0	0	0	0	0	0	0
K											0	3.0	1.5	1.5	1.5	1.5	0	0	0	0
L												0	1.5	1.5	1.5	1.5	0	0	0	0
M													0	2.5	2.5	2.5	0	0	0	0
N														0	2.5	2.5	0	0	0	0
O															0	2.5	0	0	0	0
P																0	0	0	0	0
Q																	0	2.0	2.0	2.0
R																		0	2.0	2.0
S																			0	2.0
T																				0

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FIG. 15

COREGULATED PAIRS

A + B, A + C, A + D
B + C, B + D
C + D, C + G, C + H
D + G, D + H
E + F, E + G, E + H
F + G, F + H
G + H
I + J, I + K, I + L
J + K, J + L
K + L, K + M, K + N, K + O, K + P
L + M, L + N, L + O, L + P
M + N, M + O, M + P
N + O, N + P
O + P
Q + R, Q + S, Q + T
R + S, R + T
S + T

70

FIG. 16

COREGULATED CLUSTERS

1. A + B, A + C, A + D, B + C, B + D, C + D, C + G, C + H, D + G, D + H, E + F, E + G, E + H, F + G, F + H, G + H

2. I + J, I + K, I + L, J + K, J + L, K + L, K + M, K + N, K + O, K + P, M + N, M + O, M + P, N + O, N + P, O + P

3. Q + R, Q + S, Q + T, R + S, R + T, S + T

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FIG. 17

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LINKAGE ROUTINE

START

EXECUTE COEXPRESSION ROUTINE AS A CALLED SUBROUTINE
<u>240</u>

EXECUTE COREGULATION ROUTINE AS A CALLED SUBROUTINE
<u>242</u>

PRODUCE AND STORE A LINKAGE COEFFICIENT FOR EACH KINASE PAIR (K1, K2),

$$LC(K1, K2) = \frac{CRC(K1, K2)}{CEC(K1, K2)}$$

<u>244</u>

PRODUCE SORTED PAIR LIST OF KINASE PAIRS (K1, K2) FOR WHICH LC (K1, K2) $\geq$ THRESHOLD
<u>250</u>

ADDRESS 1ST KINASE IN PAIR LIST
<u>252</u>

PRODUCE NEW LINKAGE GROUP LIST, ADD ADDRESSED KINASE K_A TO LIST
<u>254</u>

ADD TO GROUP LIST ALL OTHER KINASES K_X FOR WHICH LINKAGE TO ADDRESSED KINASE $LC(K_A, K_X) \geq$ THRESHOLD
<u>256</u>

DELETE FROM GROUP LIST EVERY KINASE K_X FOR WHICH LINKAGE TO AT LEAST ONE OTHER KINASE K_Y IN GROUP LIST $LC(K_X, K_Y)$ < THRESHOLD
<u>258</u>

FIG. 18

ALL KINASES ADDRESSED?
<u>260</u>

Y

DELETE REDUNDANT GROUPS; STORE
<u>264</u>

OUTPUT LINKED KINASE GROUPS
<u>266</u>

N

ADDRESS NEXT KINASE IN PAIR LIST
<u>262</u>

END

LINKAGE COEFFICIENTS STORE

KINASE	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
A	0	21.3	5.3	3.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
B		0	4.4	7.3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
C			0	25.9	0	0	0.9	0.9	0	0	0	0	0	0	0	0	0	0	0	0
D				0	0	0	0.9	0.9	0	0	0	0	0	0	0	0	0	0	0	0
E					0	24.2	1.7	1.5	0	0	0	0	0	0	0	0	0	0	0	0
F						0	1.6	1.6	0	0	0	0	0	0	0	0	0	0	0	0
G							0	20	0	0	0	0	0	0	0	0	0	0	0	0
H								0	0	0	0	0	0	0	0	0	0	0	0	0
I									0	31.1	33.3	18.2	0	0	0	0	0	0	0	0
J										0	13.3	14.3	0	0	0	0	0	0	0	0
K											0	66.7	6.1	6.5	6.4	6.5	0	0	0	0
L												0	6.1	6.1	6.8	6.4	0	0	0	0
M													0	62.5	33.3	125	0	0	0	0
N														0	29.4	125	0	0	0	0
O															0	33.3	0	0	0	0
P																0	0	0	0	0
Q																	0	24.1	25	43.5
R																		0	27.4	54.1
S																			0	30.3
T																				0

248 246 249 74

FIG. 19

PAIR NUMBER	LINKAGE COEFFICIENT	KINASE PAIR
1	125	M, P
2	125	N, P
3	66.7	K, L
4	62.5	M, N
5	54.1	R, T
6	43.5	Q, T
7	33.3	I, K
8	33.3	M, O
9	33.3	O, P
10	31.1	I, J
11	30.3	S, T
12	29.4	N, O
13	27.4	R, S
14	25.9	C, D
15	25	Q, S
16	24.2	E, F
17	24.1	Q, R
18	21.3	A, B
19	20	G, H
20	18.2	I, L
21	14.3	J, L
22	13.3	J, K
23	7.3	B, D
24	6.8	L, O
25	6.5	K, N
26	6.5	K, P
27	6.4	K, O
28	6.4	L, P
29	6.1	K, M
30	6.1	L, M
31	6.1	L, N
32	5.3	A, C
33	4.4	B, C
34	3.6	A, D
35	1.7	E, G
36	1.6	F, G
37	1.6	F, H
38	1.5	E, H
39	0.9	C, G
40	0.9	C, H
41	0.9	D, G
42	0.9	D, H

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FIG. 20

1. A, B, C, D

2. C, D, G, H

3. E, F, G, H

4. I, J, K, L

5. K, L, M, N, O, P

6. Q, R, S, T

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FIG. 21